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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/810,486	03/26/2004	Mitsuru Furusawa	690116.401C1	8553

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EXAMINER

BURKHART, MICHAEL D

ART UNIT PAPER NUMBER

1633

DATE MAILED: 08/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/810,486	FURUSAWA, MITSURU	
	Examiner	Art Unit	
	Michael D. Burkhart	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 07 June 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-124 is/are pending in the application.
- 4a) Of the above claim(s) 3,5,32,39,40,48,50,77,84,85 and 95-124 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 2, 4, 6-31, 33-38, 41-47, 49, 51-76, 78-83, 86-94 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 3/26/2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>11/12/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-94, in the reply filed on 6/7/2006 is acknowledged. Applicants' election of species (a)-(h) is also acknowledged, although the claims readable upon the elected species were not identified in the election. Claims 3, 5, 48, and 50 are withdrawn as not readable upon the elected species of a higher error prone frequency. Claims 32, 39, 40, 77, 84, and 85 are withdrawn as not readable upon the elected species of a yeast cell.

Claims 3, 5, 32, 39, 40, 48, 50, 77, 84, 85 and 95-124 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/7/2006.

Information Disclosure Statement

The information disclosure statement filed 11/12/2004 fail to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each reference listed that is not in the English language. The references published in Japanese have been lined through and not considered.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 3/28/2003. It is noted, however, that applicant has not filed a certified copy of the 2003-092898 application as required by 35 U.S.C. 119(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 4, 6-15, 20-31, 33-38, 41-47, 49, 51-60, 65-76, 78-83, and 86-94 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 1, 45, and 90 do not recite any positive process steps, rendering the method steps encompassed by the invention unclear. The only step recited in claim 1, "regulating an error-prone frequency of gene replication" is carried out by the cell itself and requires no active step by the user. Claims 40 and 80 recite the same step outlined above and add the step of "reproducing the resultant cell." Again, this is a step carried out by any dividing, cultured cell, and not a step necessarily performed by the user. Even if one were to presume the claimed methods included a step of transforming the cells with an error-prone DNA polymerase (i.e. an active step), the claims as instantly worded merely describe activities performed by the cells after any such transformation, not any active process steps. It would be remedial to amend the claims to recite active process steps. This rejection affects all dependent claims not reciteing an active step.

Claims 22 and 67 recite the number of a mismatched base that is "greater by at least one than that of a wild type of the DNA polymerase." As currently worded, the claim indicates that the DNA polymerase comprises a mismatched base. Because DNA polymerase (or any other protein) does not consist of nucleotides or base pairs, it is unclear how a wild-type DNA

polymerase could have more bases than any other DNA polymerase. Therefore, the metes and bounds of the claimed subject matter are unclear.

Claim 51-53 recite the limitation "the error-prone frequencies" in line 1. There is insufficient antecedent basis for this limitation in the claim. Parent claim 45 recites only a single error-prone frequency. For further prosecution purposes, the claims will be read as dependent upon claim 49.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 6-19, 22-31, 33-38, 41-47, 49, 51-64, 67-76, 78-83, and 86-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods using yeast DNA polymerase δ with a higher error-prone frequency than wild-type DNA polymerase δ and wherein the polymerase provides mismatched bases at a frequency of 10^{-6} or greater, does not reasonably provide enablement for methods using yeast DNA polymerase δ with a lower error-prone frequency than wild-type DNA polymerase δ , methods using prokaryotic DNA polymerase δ , or methods using polymerases with an error frequency less than 10^{-6} . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art

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without undue experimentation (*United States v. Telectronics, Inc.* 8 USPQD2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is a conclusion reached by weighing several factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Unpredictability of the art and State of the Art. The art concerning regulating the conversion rate (i.e. mutation rate) of genes of a cell using yeast DNA polymerase δ (*POL3*) is unpredictable. This is because the term "regulating" encompasses altering the error-prone frequency higher or lower with respect to a given background frequency (e.g. the error-prone frequency of wild type *POL3*). However, the specification and prior art teach, through mutation, how to alter the error-prone frequency of *POL3* to a higher degree with respect to a wild type *POL3*. There are no teachings of a *POL3* with a lower error-prone frequency (i.e. with a higher fidelity or proofreading function) with respect to a wild-type *POL3*. Furthermore, there are no teachings in the specification or prior art of a method, or a *POL3*, with an error-prone frequency less than 10^{-6} . The well-known *POL3* mutants taught in the prior art are *pol3-01* and *pol3-t*, the same as used by applicants in the instant specification (see Examples 1 and 2 of the specification, Morrison et al and Kokoska et al as cited in the USC 102 rejections below), and both have an error-prone frequency higher than wild-type (roughly 10^{-8} as reported by Morrison et al). Kokoska et al teach a number of additional temperature-sensitive *POL3* mutants, but again, all have an error-prone frequency greater than wild-type. Furthermore, neither the specification nor the prior art reveal any prokaryotic DNA polymerase δ , rather, the prokaryotic DNA polymerases are DNA polymerase I, II, and III, see ¶ [0287] of the publication of the instant specification. Therefore, the state of the art regarding regulating the conversion rate of genes of

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a cell using yeast *POL3* having a lower error-prone frequency with respect to a wild-type *POL3*, is poorly developed. The state of the art regarding methods using a *POL3* with an error-prone frequency less than 10^{-6} or a prokaryotic DNA polymerase δ is also poorly developed. The development of such methods, prokaryotic DNA polymerase δ , and mutations in *POL3* with the claimed function and properties would have to be done empirically.

Number of working examples. Applicants have provided no working examples of methods wherein the error-prone frequency of *POL3* is regulated such that it is lower than that found in a cell with a wild-type *POL3*. There are no working examples of a *POL3* with a mutation rate of less than 10^{-6} or a prokaryotic DNA polymerase δ .

Amount of guidance. Applicants provide no direction or guidance for preparing a *POL3* with an error-prone frequency that is lower than a wild-type *POL3*, a *POL3* with a mutation rate of less than 10^{-6} or prokaryotic DNA polymerase δ . The specification requires the skilled artisan to practice trial and error experimentation to prepare and determine which (if any) *POL3* mutants will function as claimed and to discover a prokaryotic DNA polymerase δ .

Scope of the invention. The claims are broad in nature and read on regulating the mutation rate of a cell either higher or lower using any *POL3* or a prokaryotic DNA polymerase δ .

Nature of the invention. The invention involves the unpredictable art of using and producing a *POL3* with an error-prone frequency that is lower than a wild-type *POL3*, a *POL3* with a mutation rate of less than 10^{-6} , or a prokaryotic DNA polymerase δ .

Level of skill in the art. While the level of skill in the art of using a *POL3* with an error-prone frequency greater than a wild-type *POL3* or a *POL3* with a mutation rate of greater than

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10^{-6} is high, the level of skill in the art of using a *POL3* with an error-prone frequency less than a wild-type *POL3* or a *POL3* with a mutation rate of less than 10^{-6} or a prokaryotic DNA polymerase δ is low. The unpredictability of the art, lack of guidance, broad scope of the claims and poorly developed state of the art would require that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be considered that undue and excessive experimentation would have to be conducted by the skilled artisan in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 6-14, 16, 17, 20, 21, 23-25, 28-31, 33-38, 41, 42, 45-47, 49, 51-59, 61, 65-70, 73-76, 78-83, 86, 87, and 90-94 are rejected under 35 U.S.C. 102(b) as being anticipated by Morrison et al (EMBO J., 1993, cited by applicants).

Morrison et al teach yeast strains comprising the *pol3-01* mutation of the *POL3* gene which, *inter alia*, is involved in 3'-5' exonuclease proofreading of gene replication errors (see Introduction and abstract, page 1467). Some of the diploid yeast cell strains created also comprise wild type *POL3*, all strains had wild type *POL2* and *POL1*, and others had a mutation

in *PMS1*, also involved in correcting gene replication errors (see Introduction and Table I, page 1469). The *pol3-01* error frequency is heterogeneous, at least, with respect to both wild-type *POL3* and the *pms1* mutation. Comparison of the mutation rate of the wild-type diploid strain and the *pol3-01/pol3-01 pms1/pms1* strain reveals a 38,000-fold difference in mutation rate (i.e. error frequency, Table I). Absent evidence to the contrary, the proofreading function of *POL3* detects errors in the daughter strand of a replication fork, not the parent strand, thus the *pol3-01* mutant would "provide" a difference in the number of errors of one strand (the daughter strand) relative to the parent strand. Upon growth under selective conditions, the *pol3-01* mutant provided a number of mismatch mutations in the *URA3* gene, some of which involved two changes of the wild-type sequence (Table II). The *pol3-01* mutant had a mutation rate (i.e. provided at least one mismatch) of $\sim 10^{-6}$ (Table I). The *pol3-01* mutant grew substantially as well as wild-type (compare + and - colonies in Fig. 2A). Absent evidence to the contrary the yeast cells had the three major DNA polymerases, *POL1*, *POL2*, and *POL3* or *pol3-01* all of which are involved in initiation of replication and leading and lagging strand synthesis. The cells acquired a 5-fluoro-orotic acid resistance upon selection (page 1467, second column, last ¶).

Claims 1, 2, 4, 6, 9-14, 16, 17, 20-25, 28-31, 33-38, 41-47, 49, 51, 54-59, 61, 62, 73-76, 78-83, and 86-94 are rejected under 35 U.S.C. 102(b) as being anticipated by Kokoska et al (Mol. Cell. Biol., 2000).

Kokoska et al teach yeast strains comprising temperature sensitive mutations of the *POL3* gene which, *inter alia*, is involved in 3'-5' exonuclease proofreading of gene replication errors (see abstract and page 7490, first and second columns). The yeast cell strains created had wild

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type *POL2* and *POL1*, and others comprised additional mutations in *msh3*, and/or *rad52*, also involved in correcting gene replication errors (see Table 2, and page 7490, first and second columns). The *pol3-ts1*, *pol3-ts11*, and *pol3-ts26* error frequency is heterogeneous, at least, with respect to the wild-type *POL3* and the *msh3* mutation (Table 2). Comparison of the mutation rate of the wild-type *POL3* and the *pol3-ts1 msh3* strain reveals a ~ 20-fold difference in mutation rate (i.e. error frequency, Table 2). Absent evidence to the contrary, the proofreading function of *POL3* detects errors in the daughter strand of a replication fork, not the parent strand, thus the *pol3-ts* mutants would "provide" a difference in the number of errors of one strand (the daughter strand) relative to the parent strand. Upon growth under selective conditions, the *pol3-ts* mutant provided a number of mismatch mutations in the *CAN1* gene, some of which involved more than two changes of the wild-type sequence, e.g. 16-base pair deletions (Table 3). The *pol3-ts* mutants had a mutation rate (i.e. provided at least one mismatch) of $\sim 10^{-6}$ (Table 2). The *pol3-ts1* and *pol3-ts8* mutants grew substantially as well as wild-type (Fig. 3). Absent evidence to the contrary the yeast cells had the three major DNA polymerases, *POL1*, *POL2*, and *POL3* or *pol3-01* all of which are involved in initiation of replication and leading and lagging strand synthesis. The cells acquired canavanine resistance upon selection (page 7493, second column, last ¶ and Table 2). Because the *pol3-ts* mutants are temperature sensitive, they could be regulated with temperature (page 7492, second column to page 7493).

Double Patenting

Applicant is advised that should claims 45, 91, or 92 be found allowable, claims 90, 93, and 94 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two

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claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). When examined in light of the election of yeast cells as a species, the scope of claims 45 and 90 is identical, i.e. they produce a yeast cell, which is an organism, using the same method steps. The same is true for the cells and organisms of claims 91-94, respectively, because they are produced by the same methods, i.e. the yeast cell of claims 91-92 is also an organism and no different in scope in light of the election of yeast cells as a species.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1, 2, 4, 6-14, 20-31, 33-38, 41-43, 45-47, 49, 51-59, 65-76, 78-83, 86-88, and 90-94 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 2, 4, 6-26, 28-33, 36-38, 40-42, 44, 46-66, 68-73, 76-78, and 80-84 of copending Application No. 10/684,141. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. The claims are word-for-word copies of one another, and hence are no different in scope.

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Claims 1, 2, 4, 6-14, 20-31, 33-38, 41-43, 45-47, 49, 51-59, 65-76, 78-83, 86-88, and 90-94 of this application conflict with claims 1, 2, 4, 6-26, 28-33, 36-38, 40-42, 44, 46-66, 68-73, 76-78, and 80-84 of Application No. 10/684,141. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 44 and 89 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 39 and 79 of copending Application No. 10/684,141. Although the conflicting claims are not identical, they are not patentably distinct

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from each other because all the limitations of instant claims 39 and 79 are recited in the claims of the '141 patent, although the claims of the instant application are broader in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

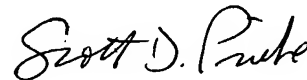
No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael D. Burkhart whose telephone number is (571) 272-2915. The examiner can normally be reached on M-F 8AM-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael D. Burkhart
Examiner
Art Unit 1633



SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER